

IN THE CLAIMS

Please amend the claims as follows:

1. (Currently Amended) A method of inducing tumor cell death in a human patient by inducing a type 1 inflammatory response in a solid tumor, the method comprising
 - i) locally administering an antigen-releasing agent to a solid tumor in the patient, whereby a tumor antigen is released from cells of the tumor;
 - ii) locally administering to the tumor a leukocyte attractant, whereby leukocytes are induced to infiltrate the tumor; and
 - iiib) locally administering to the tumor interferon-gamma (IFN-g) as a first type 1 inflammatory response promoting agent and a second type 1 inflammatory response-(IR1-)promoting agent selected from the group consisting of tumor necrosis factor-beta (TNF-b), tumor necrosis factor-alpha (TNF-a), interleukin-2 (IL-2), interleukin-12 (IL-12), and a mixture thereof whereby a type 1 inflammatory response is induced in the tumor and tumor cell death is induced.
2. (Original) The method of claim 1, wherein the antigen-releasing agent is a tumor debulking agent.
3. (Currently Amended) The method of claim 1, wherein the antigen-releasing agent comprises an agent selected from the group consisting of a proteolytic enzyme, an apoptosis-inducing agent, electrical current, ~~a strong an acid, and a strong base;~~ and a mixture thereof.
4. (Currently Amended) The method of claim 3, wherein the antigen-releasing agent comprises a proteolytic enzyme selected from the group consisting of trypsin, chymotrypsin, pepsin, ~~and collagenase,~~ and a mixture thereof.
5. (Original) The method of claim 3, wherein the antigen-releasing agent comprises only one proteolytic enzyme.

6. (Original) The method of claim 3, wherein the antigen-releasing agent comprises at least two proteolytic enzymes.
7. (Original) The method of claim 3, wherein the antigen-releasing agent comprises an alkylphospholipid.
8. (Original) The method of claim 7, wherein the alkylphospholipid is an alkylphosphocholine.
9. (Currently Amended) The method of claim 7, wherein the alkylphosphocholine is selected from the group consisting of hexadecylphosphocholine, edelfosine, and a mixture thereof ~~and edelfosine~~.
10. (Original) The method of claim 3, wherein the antigen-releasing agent is electrical current delivered by way of electrodes inserted into the tumor.
11. (Currently Amended) The method of claim 3, wherein the antigen-releasing agent comprises a ~~strong~~ an acid selected from the group consisting of hydrochloric acid ~~and sulfuric~~, sulfuric acid, and a mixture thereof.
12. (Currently Amended) The method of claim 3, wherein the antigen-releasing agent comprises a ~~strong~~ base selected from the group consisting of sodium ~~hydroxide and~~ hydroxide, potassium hydroxide, and a mixture thereof.
13. (Original) The method of claim 1, wherein the antigen-releasing agent is administered to the tumor at least two hours before administering the leukocyte attractant to the tumor.
14. (Original) The method of claim 1, wherein the antigen-releasing agent and the leukocyte attractant are co-administered to the tumor.

15. (Original) The method of claim 1, wherein the antigen-releasing agent is administered to the tumor at least two hours before administering IFN-g to the tumor.

16. (Original) The method of claim 1, wherein the antigen-releasing agent and the IFN-g are co-administered to the tumor.

17. (Original) The method of claim 1, wherein the leukocyte attractant comprises a monocyte attractant.

18. (Currently Amended) The method of claim 17, wherein the monocyte attractant is selected from the group consisting of MCP-1, MCP-2, MCP-3, ~~and MCP-4~~, and a mixture thereof.

19. (Original) The method of claim 1, wherein the leukocyte attractant comprises a T cell attractant.

20. (Currently Amended) The method of claim 19, wherein the T cell attractant is selected from the group consisting of RANTES, IP-10, ~~and Mig~~, and a mixture thereof.

21. (Original) The method of claim 1, wherein the leukocyte attractant comprises a granulocyte attractant.

22. (Currently Amended) The method of claim 21, wherein the granulocyte attractant is selected from the group consisting of interleukin-8, ~~granular component P-2~~ granulocyte chemotactic protein-2, growth-related oncogen-1, growth-related oncogen-2, growth-related oncogen-3, neutrophil activated protein, ~~and neurotactin~~, and a mixture thereof.

23. (Original) The method of claim 21, wherein the granulocyte attractant is a eosinophil attractant.

24. (Original) The method of claim 23, wherein the eosinophil attractant is eotaxin.

25. (Original) The method of claim 1, wherein the leukocyte attractant is co-administered with at least one of IFN-g and the second IR1-promoting agent.

26. (Original) The method of claim 1, wherein the leukocyte attractant and at least one of IFN-g and the second IR1-promoting agent are administered not more than two hours apart.

27. (Original) The method of claim 1, wherein the leukocyte attractant and at least one of IFN-g and the second IR1-promoting agent are administered more than two hours apart.

28. (Original) The method of claim 1, wherein the leukocyte attractant and at least one of IFN-g and the second IR1-promoting agent are co-administered.

29. (Currently Amended) The method of claim 1, ~~wherein~~ which further comprises administering at least one additional ~~the second~~ IR1-promoting agent is selected from the group consisting of interleukin-2 (IL-2), interleukin-12 (IL-12), tumor necrosis factor-alpha (TNF-a), and tumor necrosis factor-beta (TNF-b), and a mixture thereof.

30. (Cancelled)

31. (Cancelled)

32. (Cancelled)

33. (Currently Amended) The method of claim 1, wherein multiple aliquots of each of IFN-g ~~and~~ the second and the additional IR1-promoting agents are administered to the patient, and wherein at least 48 hours elapse between aliquots.

34. (Currently Amended) The method of claim 1, wherein IFN-g ~~and the~~ the second and the additional IR1-promoting agent are co-administered.

35. (Currently Amended) The method of claim 1, wherein IFN-g ~~and~~ the second and the additional IR1-promoting agents are separately administered not more than two hours apart.

36. (Currently Amended) The method of claim 1, wherein IFN-g ~~and~~ the second and the additional IR1-promoting agents are separately administered more than two hours apart.

37. (Original) The method of claim 1, further comprising

- iii) locally administering to the tumor a type 1 lymphocyte attractant in order to sustain the type 1 inflammatory response.

38. (Currently Amended) The method of claim 37, wherein the type 1 lymphocyte attractant is selected from the group consisting of RANTES, IP-10, ~~and~~ Mig, and a mixture thereof.

39. (Currently Amended) The method of claim 37, wherein ~~the two~~ type 1 lymphocyte ~~attractant~~ attractants are locally administered and wherein the type 1 lymphocyte attractants are comprises IP-10 and Mig.

40. (Original) The method of claim 37, further comprising

- iv) sustaining the type 1 inflammatory response by locally administering autologous leukocytes to the tumor.

41. (Original) The method of claim 37, further comprising

- iv) administering a memory cell-inducing agent to the patient after inducing the type 1 inflammatory response, whereby production of anti-tumor type 1 immune memory cells is enhanced.

42. (Currently Amended) The method of claim 41, further comprising

- v) supplementing the patient's nutrition with a nutrient selected from the group consisting of a vitamin, a mineral, and a mixture thereof ~~and a mineral~~.

43. (Original) The method of claim 37, further comprising

- iv) supplementing the patient's nutrition with a nutrient selected from the group consisting of a vitamin, a mineral, and a mixture thereof ~~and a mineral~~.

44. (Original) The method of claim 1, further comprising

- iii) locally administering autologous leukocytes to the tumor.

45. (Original) The method of claim 44, wherein the autologous leukocytes are obtained from the patient and expanded prior to locally administering them to the tumor.

46. (Currently Amended) The method of claim 44, wherein the autologous leukocytes are obtained from the patient and contacted with ~~an independently selected one or more~~ IR1-promoting agent prior to locally administering them to the tumor.

47. (Currently Amended) The method of claim 44, wherein the autologous leukocytes are obtained from the patient, expanded ex vivo, and contacted with ~~an independently selected one or more~~ IR1-promoting agent prior to locally administering them to the tumor.

48. (Currently Amended) The method of claim 47, wherein the leukocytes are contacted with both the ~~an independently selected one or more~~ IR1-promoting agent and with at least one of interferon-alpha (IFN-a) and IL-12 prior to locally administering them to the tumor.

49. (Original) The method of claim 44, further comprising

- iv) administering a memory cell-inducing agent to the patient after inducing the type 1 inflammatory response, whereby production of anti-tumor type 1 immune memory cells is enhanced.

50. (Currently Amended) The method of claim 49, further comprising

- v) supplementing the patient's nutrition with a nutrient selected from the group consisting of a vitamin, a mineral, and a mixture thereof ~~and a mineral~~.

51. (Currently Amended) The method of claim 44, further comprising

iv) supplementing the patient's nutrition with a nutrient selected from the group consisting of a vitamin, a mineral, and a mixture thereof ~~and a mineral~~.

52. (Original) The method of claim 1, further comprising

iii) administering a memory cell-inducing agent to the patient after inducing the type 1 inflammatory response, whereby production of anti-tumor type 1 immune memory cells is enhanced.

53. (Currently Amended) The method of claim 52, wherein the memory cell-inducing agent is selected from the group consisting of interleukin-15 (IL-15), IFN-a, and a mixture thereof ~~and IFN-a~~.

54. (Original) The method of claim 52, wherein the memory cell-inducing agent is IL-15.

55. (Original) The method of claim 52, wherein the memory cell-inducing agent is IFN-a.

56. (Currently Amended) The method of claim 52, wherein the memory cell-inducing agent is administered after the tumor shrinks to less than 10 percent of its ~~size~~ size, immediately prior to administration of the ~~antigen-releasing~~ memory cell inducing agent.

57. (Currently Amended) The method of claim 1, further comprising supplementing the patient's nutrition with a nutrient selected from the group consisting of a vitamin, a mineral, and a mixture thereof ~~and a mineral~~.

58. (Currently Amended) The method of claim 57, wherein the vitamin is selected from the group consisting of vitamins A, B, C, D, ~~and E~~, and a mixture thereof.

59. (Original) The method of claim 58, wherein the vitamin is vitamin C and wherein the patient's nutrition is supplemented such that the patient receives from 200 to 400 milligrams of vitamin C daily.

60. (Original) The method of claim 58, wherein the vitamin is vitamin E and wherein the patient's nutrition is supplemented such that the patient receives from 200 to 400 international units of vitamin E daily.

61. (Currently Amended) The method of claim 57, wherein the mineral is selected from the group consisting of selenium, zinc, calcium, magnesium, iron, ~~and copper,~~ and a mixture thereof.

62. (Original) The method of claim 61, wherein the mineral is selenium and wherein the patient's nutrition is supplemented such that the patient receives from 200 to 400 micrograms of selenium daily.

63. (Original) The method of claim 61, wherein the mineral is zinc and wherein the patient's nutrition is supplemented such that the patient receives from 15 to 100 milligrams of zinc daily.

64. (Original) The method of claim 57, wherein the patient's nutrition is supplemented beginning at least on the same day that the antigen-releasing agent is administered to the tumor, and continuing through at least the same day that IFN-g is administered to the tumor.

65. (Original) The method of claim 57, wherein the patient's nutrition is supplemented beginning at least five days before the antigen-releasing agent is administered to the tumor, and continuing through at least three days after the day that IFN-g is administered to the tumor.

66. (Currently Amended) A method of inducing tumor cell death in a human patient by inducing a type 1 inflammatory response in a solid tumor, the method comprising

- i) supplementing the patient's nutrition with a nutrient selected from the group consisting of a vitamin, a mineral, and a mixture thereof ~~and a mineral~~;
- ii) locally administering an antigen-releasing agent to a solid tumor in the patient, whereby a tumor antigen is released from cells of the tumor;

thereafter

iiia) locally administering to the tumor a leukocyte attractant, whereby leukocytes are induced to infiltrate the tumor; and

iiib) locally administering to the tumor interferon-gamma (IFN-g) as a first type 1 inflammatory response promoting agent and a second type 1 inflammatory response-(IR1-)-promoting agent, selected from the group consisting of tumor necrosis factor-beta (TNF-b), tumor necrosis factor-alpha (TNF-a), interleukin-2 (IL-2), interleukin-12 (IL-12), and a mixture thereof whereby a type 1 inflammatory response is induced in the tumor;

thereafter

iv) sustaining the type 1 inflammatory response by

iva) locally administering to the tumor a type 1 lymphocyte attractant,

ivb) locally administering autologous leukocytes to the tumor, or

ivc) both iva) and ivb);

and thereafter

v) administering a memory cell-inducing agent to the patient after inducing the type 1 inflammatory response, whereby production of anti-tumor type 1 immune memory cells is enhanced and tumor cell death is induced.

67-80. (Canceled)

81. (Currently Amended) A method of inducing a type 1 inflammatory response at the site of a solid tumor in a human patient, the method comprising locally co-administering

i) ~~locally administering~~ an antigen-releasing agent to the tumor;

iiia) ~~locally administering~~ to the tumor a leukocyte attractant; and

iiib) ~~locally administering~~ to the tumor interferon-gamma (IFN-g) as a first type 1 inflammatory response promoting agent and a second type 1 inflammatory response-(IR1-)-promoting agent selected from the group consisting of tumor necrosis factor-beta (TNF-b), tumor necrosis factor-alpha (TNF-a), interleukin-2 (IL-2), interleukin-12 (IL-12), and a mixture thereof.

Application No. 09/756,978
Reply to Office Action of September 2, 2004

82 and 83. (Canceled)